REMARKS

Claims 23-44 remain pending in this application. Reconsideration of the merits of the application in light of the remarks below is respectfully requested.

I. Rejection under 35 USC § 112, first paragraph

Claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 have been rejected under 35 USC § 112, first paragraph as allegedly lacking an enabling description. Applicants respectfully traverse the rejection.

The Examiner stated, "Applicant fails to set forth the criteria that allows the skilled artisan to identify those HIV strains 'resistant to a chemotherapeutic agent'. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation." In addition the Examiner stated, "The instant claims read on all HIV strains 'resistant to chemotherapeutic agent', necessitating an exhaustive search for the embodiments suitable to practice the claimed invention."

A. The Test for Undue Experimentation

"The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 279 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)." MPEP § 2164.01

"The test for what constitutes undue experimentation is not merely quantative, since a considerable amount of experimentation is permissible, if it is merely routine. . ." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. *See also* MPEP § 2164.06. Further, a patent need not disclose what is well known in the art. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). See also MPEP § 2164.01.

As the Examiner indicated, the Federal Circuit in *In re Wands* set forth eight factors for considering whether a specification is enabling. The eight factors are:

1. The Quantity of Experimentation Necessary
2. The Amount of Direction or Guidance Provided
3. The Presence or Absence of Working Examples
4. The Nature of the Invention
5. The State of the Prior Art
6. The Relative Skill of Those in the Art
7. The Predictability of the Art
8. The Breath of the Claims

B. Practice of the Invention as Claimed in Claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 Does Not Require Undue Experimentation

Nothing more than permissible routine testing as would be understood by one skilled in the art may be required to practice the invention as claimed invention

The identification of HIV strains resistant to a chemotherapeutic agent and of such chemotherapeutic agents is accomplished by standard techniques well known in the art. For example, one can monitor CD4 cell counts, immune complex-dissociated p24 antigen, viral phenotype, and viral load in plasma of a patient receiving an anti-HIV chemotherapeutic agent. See, *e.g.*, Rusconi et al., *Antivir. Ther.*, 1(4):211-219, Dec. 1996, at 211 (abstract). Such methods are well known and routine in the art. Further, the Examiner himself, in an Office Action dated September 21, 2001 (Paper No. 14) indicated an alternative and well-known way of identifying the presence of a resistant strain of HIV; namely, a physician could identify a patient harboring a resistant HIV strain by the mere fact that the patient is not responding to anti-HIV chemotherapy. *See* Paper No. 14 at p. 3. Identification of which chemotherapeutic agents a HIV virus is resistant to flows from the techniques described above and requires no additional testing. That is, identification of a resistant to a chemotherapeutic agent necessarily results in identification of a chemotherapeutic agent to which the virus is resistant, thus no additional testing is required.

Resistant HIV viruses can also be identified through well-known cell culture techniques, as indicated in the present specification. One can, *e.g.*, measure the concentration of a chemotherapeutic agent required to inhibit replication of a sensitive

HIV strain and compare that to the concentration required to inhibit replication of a different strain. If the different strain is less sensitive to the chemotherapeutic agent than the sensitive strain, the different strain is considered sensitive. See, *e.g.*, Table 2 at page 12 of the specification where HTLV IIIB is indicative of a sensitive strain and RT-MDR is indicative of a resistant strain.

Further, one can identify resistant HIV by determining whether the HIV contain a known mutation resulting in resistance to known chemotherapeutic agents. Such mutations are discussed at, for example, page 2, lines 1-4 of the present specification. These mutants are readily identified through well-known techniques, such as nucleotide sequencing. See, *e.g.*, Masquelier et al., *Antivir. Ther.*, 4(2): 69-77, 1999 (abstract).

The analysis of the *Wands* factors as applied to claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 of the present application is as follows:

1. The quantity of experimentation necessary

As mere routine experimentation is required to practice the claimed invention commensurate with the scope of claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42, the quantity of experimentation is not undue. Such a conclusion is required by, e.g., MPEP § 2164.06: "The test for what constitutes undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . ." citing *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Some examples of routine experimentation resulting in identification of a strain of HIV resistant to a chemotherapeutic agent are discussed above. For example, mere monitoring of CD4 cell counts, immune complex-dissociated p24 antigen, viral phenotype, and viral load in plasma of a patient receiving an anti-HIV chemotherapeutic agent will allow one skilled in the art to determine whether a HIV virus is resistant to the anti-HIV chemotherapeutic agent. Such techniques are well known and a routine part of treatment of an HIV infection. In addition, simply monitoring patient outcome can be an indicator of whether a patient is harboring a resistant strain of HIV. Further, routine cell culture experimentation, where the ability of a chemotherapeutic agent to inhibit HIV replication is compared between two or more cell lines infected with different strains of

HIV, can be used to identify strains of HIV that are resistant to the chemotherapeutic agent. One skilled in the art can also identify resistant HIV by determining whether the HIV contain a known mutation resulting in resistance to known chemotherapeutic agents.

Applicants assert that none of the above experimentation and well known techniques are complex. However, to the extent that they are determined by the Examiner to be complex, such a determination cannot result in a finding that such experimentation is undue because one of skill in the art typically engages in such experimentation:

> "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub. nom., Massacheutts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404."
>
> MPEP § 2164.01

2. The amount of direction or guidance provided

"A patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01, citing *In re Buchner*, 929 F.2d 660,661, 18 USPQ2d. 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 91, 94 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). As discussed above, one of skill in the art, through mere routine experimentation using well-known techniques, could readily identify which strains of HIV are resistant to a chemotherapeutic agent and those chemotherapeutic agents to which the HIV are resistant. As such techniques and experimentation are well known in the art, it is appropriate for the specification to omit a discussion of how to perform such experimentation using such techniques. One of skill in the art, upon reading the specification, would understand the distinction between sensitive and

resistant strains of HIV and, based on knowledge already in their possession, would be able to identify those strains that are resistant to a chemotherapeutic agent.

3. The presence or absence of working examples

While neither 35 U.S.C. § 112, first paragraph, nor any of the other sections of the Patent Statute or Patent Rules require that a specific working example be disclosed, Applicants have provided working examples showing the effectiveness of the two compounds within the claimed method against several strains of HIV resistant to one or more chemotherapeutic agent. See, *e.g.*, Table 2 at page 12 of the specification. Disclosure of such working examples is clearly sufficient for purposes of enablement.

4. The nature of the invention

The nature of the claimed invention involves inhibition of replication of drug-resistant HIV with the two specific compounds within the claims. The two specific compounds lie at the heart of the invention, due to their increased efficacy, relative to known and approved anti-HIV chemotherapeutics. The identification of compounds having the properties associated with the two specific compounds is indeed a difficult task. However, as discussed above, how to identify resistant strains of HIV and agents against which the HIV are resistant, which the Examiner has indicated as lacking an enabling disclosure, are so well known in the art that Applicants are perplexed as to why the Examiner rejected the claims as lacking an enabling disclosure.

5. The state of the prior art

The principles underlying treating HIV infection and inhibiting HIV replication with non-nucleoside inhibitors of reverse transcriptase is well known. See, e.g., Shafer et al. "A guide to HIV-1 reverse transcriptase and protease sequencing for drug resistance studies" in *Human Retroviruses and AIDS,* Theoretical Biology and Biophysics. Los Alamos National Laboratories, 2001, pp. 1-51 (particularly pages 5-11). However, it is the identification of compounds useful against resistant strains of HIV that is difficult. Surprisingly, Applicants have identified two such compounds and methods of their use is claimed. Applicants have disclosed the inventive aspect of the claimed invention, namely

identification of two compounds useful against drug-resistant HIV. The identification of resistant strains of HIV and agents against which the strains are resistant is known in the art and well within the ability of one of skill in the art.

6. The relative skill of those in the art

The level of skill in the art of resistant HIV was high at the time the present application was filed. For example, a PubMed database search for publications prior to March of 1993 resulted in 1561 publications related to "drug resistant HIV." A copy of the first few pages of the search are enclosed.

7. The predictability of the art

As indicated above, the difficulty in the resistant HIV art is in identifying compounds useful for treatment of resistant HIV and inhibition of HIV replication. Thus, Applicants' claims are limited to only two compounds shown by the instant specification to possess superior properties to known and approved anti-HIV compounds. The predictability of the art with regard to the ability to identify resistant HIV strains and the agents against which they are resistant is quite high. As indicated above, the techniques for such identification are well known and are quite accurate and predictable in their results.

8. The breath of the claims

The breadth of the claims at issue is quite narrow. The claims are directed to a method of inhibiting replication of drug-resistant HIV strains using only two specified compounds. The specification teaches the effectiveness of these two compounds in inhibiting replication of drug-resistant HIV and in doing so provides guidance for how to test the effectiveness of the two compounds for effectiveness in inhibiting replication of drug-resistant HIV. As discussed above, the identification of drug resistant strains of HIV and the chemotherapeutic agents to which they are resistant is well within the abilities of one skilled in the art .

C. Summary

Applicants assert that the specification provides adequate guidance with regard to how to make and use the invention commensurate in scope with claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42. These claims recite only two compounds, which the specification teaches as being effective for inhibiting replication of drug-resistant HIV. The specification teaches how to make and use the two compounds according to the claims at issue. However, the Examiner contends that the specification lacks an enabling disclosure for failing to set forth the criteria that allows the skilled artisan to identify those HIV strains resistant to a chemotherapeutic agent. As indicated above, one of skill in the art through routine, and well-known experimentation can readily ascertain whether a strain of HIV is resistant to a chemotherapeutic agent. In light of the specification and the level of skill in the art, Applicants respectfully assert that a skilled artisan, upon reading the specification, could practice the invention commensurate in scope with the claims without undue experimentation.

Withdrawal of the rejection is respectfully requested.

If the Examiner maintains the rejection, Applications request clarification as to why claims 25 and 26, and their respective dependent claims, claims 30, 31, 35, 36, 41, and 42, were rejected for failing "to set forth the criteria that allows the skilled artisan to identify those HIV strains 'resistant to a chemotherapeutic agent'" when the claims do not recite "resistant to a chemotherapeutic agent."

II. Rejection under 35 USC § 112, second paragraph

Claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 have been rejected under 35 USC § 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse the rejection.

The Examiner rejected claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 as being indefinite for reciting the phrase "resistant to a chemotherapeutic agent." The Examiner stated that the phrase was indefinite because criteria for defining HIV strains resistant to a chemotherapeutic agent are not disclosed in the specification.

Applicants assert that the phrase "resistant to chemotherapeutic agent" in the context of HIV resistant strains is clear and definite because such language is well-known and understood in the art. A search of the literature indicates at least 1561 journal articles discussing drug-resistant HIV were published prior to March 1993. See discussion above under section I(B)(6). In addition, what is meant by "resistant to chemotherapeutic agent" is discussed throughout the specification. For example, page 1, lines 24-29 discusses that mutations and selective pressure can result in drug resistant HIV strains, and page 2, lines 1-4 presents examples of known resistant strains. The phrase "resistant to chemotherapeutic agent" is well understood by those skilled in the art and adequately discussed in the specification, thus Applicants assert that claims 23, 25, 26, 29, 30, 31, 34, 35, 36, 39, 41 and 42 are clear and definite.

Withdrawal of the rejection is respectfully requested.

If the Examiner maintains the rejection, Applications request clarification as to why claims 25 and 26, and their respective dependent claims, claims 30, 31, 35, 36, 41, and 42, were rejected for as being indefinite for reciting "resistant to a chemotherapeutic agent" when the claims do not recite "resistant to a chemotherapeutic agent."

III. Rejection under 35 USC § 103

A. Claims 23-44

Claims 23-44 have been rejected under 35 USC 103 as allegedly being unpatentable over Lind et al. Applicants traverse the rejection.

The Examiner stated that "Lind et al. . . . teach the claimed compounds as old and well known in the art" and that these compounds can be useful for treatment of HIV. The Examiner, pointing to page 3, lines 20-24 of Lind et al., further stated that Lind et al. suggest that their compounds can be useful for treating resistant HIV. The Examiner thus concluded that it would be obvious to use the compounds disclosed by Lind et al. as anti-HIV agents, including resistant strains.

Applicants continue to assert one would not be motivated to select any of the two compounds recited in the present claims for treatment of drug resistant HIV in light of the

teachings of Lind et al. Lind et al. teach that compounds having a structure most similar to those recited in claims 23-44 of the present application are far inferior to other compounds disclosed by Lind et al. for inhibition of replication of a non-drug resistant strain of HIV. Based on this disclosure, one neither would be motivated to use the compounds recited in present claims 23-44 to treat resistant strains of HIV nor would have a reasonable expectation of success.

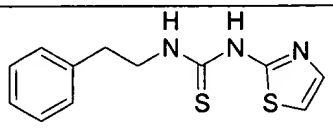
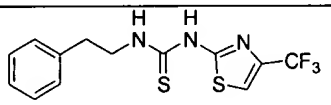
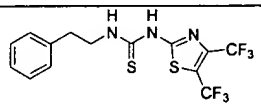
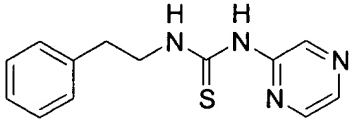
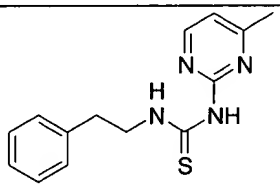
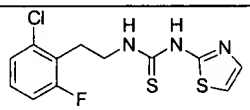
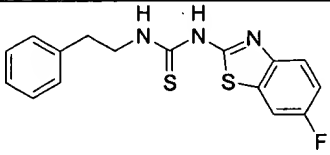
The Examiner points to page 3, lines 20-24 of Lind et al. as providing motivation to use the compounds recited in the present claims against resistant strains of HIV. The area of the Lind patent publication to which the Examiner points reads as follows:

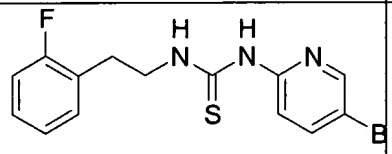
> Unfortunately, many of the compounds [useful for inhibiting HIV or treating AIDS] suffer from toxicity problems, lack of bioavailability or are short lived in vivo, viral resistance, or combinations thereof.
>
> WO 93/03022 at page 3, lines 21-24

Such a statement is hardly sufficient to provide one skilled in the art with motivation to use the two compounds recited in the present claims against resistant HIV when Lind et al. do not disclose any activity data for the two compounds and when Lind et al. disclose that the most structurally similar compound tested has inferior activity against non-resistant HIV.

Simply stated, nothing in Lind et al. suggests that the two compounds recited in the present claims would have the superior efficacy against resistant HIV as disclosed in the present specification. In fact, Lind et al. teach that compounds such as those recited in the present claims, *i.e.*, those having a 1-phenethyl-3-pyridin-2-yl-thiourea "core", are far inferior to other compounds for treatment or inhibition of HIV. Reproduced below is a table summarizing the results presented in Lind et al. that Applicants submitted in their two previous Responses.

Test Compound	% Inhibition of HIV-RT at below compound concentration

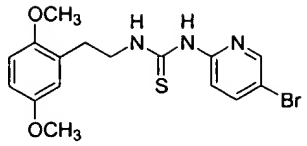
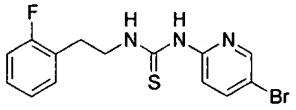
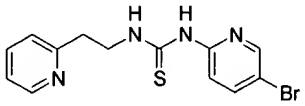
	100 ug/ml	10 ug/ml	1 ug/ml	0.1 ug/ml
 1-Phenethyl-3-thiazol-2-yl-thiourea	-	100	100	2
 1-Phenethyl-3-(4-trifluoromethyl-thiazol-2-yl)-thiourea	66	24	100	-
 1-(4,5-Bis-trifluoromethyl-thiazol-2-yl)-3-phenethyl-thiourea	99	85	71	-
 1-Phenethyl-3-pyrazin-2-yl-thiourea	100	100	4	-
 1-(4-Methyl-pyrimidin-2-yl)-3-phenethyl-thiourea	100	64	42	-
 1-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-3-thiazol-2-yl-thiourea	100	100	100	-
 1-(6-Fluoro-benzothiazol-2-yl)-3-phenethyl-thiourea	100	100	100	-

Test Compound	% Inhibition of HIV-RT at below compound concentration			
	100 ug/ml	10 ug/ml	1 ug/ml	0.1 ug/ml
 [2-(2-fluorophenylethyl)]-[2-(5-bromopyridyl)]	**6**	**2**	**0**	**-**

As shown from the table above, the data disclosed in Lind et al. indicates that 1-phenethyl-3-pyridin-2-yl-thiourea, the "core" of the compounds recited in the present claims, is considerably less effective than other compounds having different cores.

Further, Lind et al. at page 118, line 38-40 disclose Trovirdine [N-(2-pyridylethyl)-N'-(5-bromo-2-pyridyl)thiourea] as the single "especially preferred" compound. Nothing in Lind et al. would point to the two compounds in the present claims as having superior properties to Troviridine. Surprisingly, however, Applicants have discovered just that - that is, the two compounds recited in the claims 23-44, compounds having an "inferior" 1-phenethyl-3-pyridin-2-yl-thiourea "core" - are *more* effective than trovirdine in inhibiting replication of drug resistant HIV. For the Examiner's convenience, relevant portions of Table 2 of the present application is reproduced below.

RT Inhibitors	**RRT (μM)**	**HTLV IIIB WT**	**RT-MDR (74V, 41L, 106A, 215Y)**
		IC50 p24 (μM)	**IC50 p24 (μM)**

DDE236  [2-(2,5-dimethoxyphenylethyl)]-[2-(5-bromopyridyl)]-thiourea	0.1	<0.001	0.005
DDE240  [2-(2-fluorophenylethyl)]-[2-(5-bromopyridyl)]-thiourea	0.6	<0.001	0.005
Trovirdine  2-pyridylethyl-(5-bromo-2-pyridyl)-thiourea	0.8	0.007	0.02

WT=wild type.

Clearly the fact that the two compounds recited in claims 23-44 are more efficacious than trovirdine, the single "especially preferred" compound disclosed by Lind et al. is surprising and unexpected. As such, the claims 23-44 are not obvious in light of the teachings of Lind et al.

Applicants again re-iterate that new uses of compounds are patentable. Here the new use is treatment and inhibition of replication of drug resistant HIV. As applicants have continually asserted, use of a compound for treatment and/or inhibition of wild-type HIV and drug resistant HIV are different uses. Nothing in Lind et al. would lead one to select the two compounds recited in the present claims for treatment of drug resistant HIV with a reasonable expectation of success. As such claims 23-44, supported by Applicants unexpected findings, are not obvious in light of Lind et al.

Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above, Applicant respectfully requests withdrawal of the rejections and allowance of the claims. Prompt passage to issue is earnestly solicited. Should the Examiner feel a telephone interview would be helpful in advancing this case to allowance, Applicant invites the Examiner to contact their representative at the number listed below.

Respectfully submitted,

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Dated: 17 April 2003

By: Keith Campbell
Keith Campbell
Reg. No. 46,597

Enclosures:

1. Shafer et al. "A guide to HIV-1 reverse transcriptase and protease sequencing for drug resistance studies" in *Human Retroviruses and AIDS,* Theoretical Biology and Biophysics. Los Alamos National Laboratories, 2001, pp. 1-51.
2. Search regarding publications to March 1999 discussing drug resistant HIV.
3. Rusconi et al., *Antivir. Ther.*, 1(4):211-219, Dec. 1996, at 211 (abstract).
4. Masquelier et al., *Antivir. Ther.*, 4(2): 69-77, 1999 (abstract).